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Huntington Disease: Genetics and Epidemiology

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Huntington disease (HD) is an autosomal dominant disorder in which the major gene expression occurs in the central nervous system. It is characterized by the appearance of progressive chorea and dementia, usually in adult life. One tragic aspect of the disorder, due to its late age of onset and, until recently, lack of a presymptomatic marker, is that transmission of the disease to offspring invariably occurs before symptoms develop in the parent. Although the onset of symptoms and the rate of progression may vary, the prognosis is one of relentless deterioration. The major pathological features of HD are a primary loss of cells in the caudate nucleus and putamen (striatum) but other regions of the basal ganglia, hypothalamus, and brain stem are also involved. Not only is there neuronal loss but there is also a decrease in the level of a number of neurotransmitters and associated enzymes, together with abnormalities in some receptor sites. Martin [1] described the disease as "genetically programmed cell death in the human central nervous system."

HISTORY

In 1872 George Huntington [2] published his first and only scientific paper "On Chorea" and, thus, had his name used in the eponymic designation of the disease. He was not the first to describe the disease, but despite earlier descriptions, his was the first complete description of the disease, so complete that it is often referred to as classic.

An interesting aspect of the disease concerns the hereditary origin of the cases in the United States. Vessie [3] traced over 1,000 cases of HD in the United States to discover that they were descended from two brothers and another relative who emigrated from Suffolk in England (less than 50 miles from George Hun-

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tington's ancestral home) in 1630 and settled in New England. A number of descendants of this group were branded as witches; one of the more notorious examples was a granddaughter of one the first settlers who became known as the Groton Witch. Critchley [4] traced another group of New England families to the same general area in Britain. He could not determine if the two families were related. Drs. E. B. Muncey and C. B. Davenport at the Eugenics Record Office of the Carnegie Institution at Cold Spring Harbor, New York, compiled the histories of these New England families in 1913; they were published in a limited mimeographed edition by the Dight Institute of Human Genetics of the University of Minnesota in 1964 under the direction of Dr. S. C. Reed. This manuscript makes fascinating reading as it traces these families over 11 generations; it is also valuable for research on current families and linking them with others through common ancestors.

Although the families with an English derivation are the best known, there are numerous additional sources of the gene in the North American continent. A family from Nova Scotia, whose affected progenitor was of Hugenot origin, arrived from France in 1685 [5]. Critchley [4] referred to 92 cases from Ontario whose ancestors could be traced to England, Ireland, and Scotland. Among U.S. families, ancestry can be traced to most western and eastern European countries. Vessie [6] quotes Hamilton who observed choreics in Iowa and found that the HD gene could be traced directly to England, Germany, Ireland, Norway, and throughout Europe.

The disease has been reported worldwide; a number of areas other than the United States and Canada have received the HD gene through migration. Two of the better known are Venezuela [7] and Tasmania [8].

CLINICAL MANIFESTATIONS

Although HD is inherited as an autosomal dominant mutation, there is considerable variation in both phenotype and onset of symptoms. Clinically, the disease can be expressed in two different forms: the classical choreic form and the rigid form. The clinical picture of the choreic form is usually one of abnormal involuntary movements (chorea) accompanied by intellectual impairment (dementia) and a spectrum of psychiatric disturbances. The choreic movements in HD as described by Bell [9] are "aimless, forceful and complicated." These movements occur suddenly and resist efforts of patients to control them. Characteristic movements include facial grimacing and twisting and jerking of the trunk and limbs. These increase with time, and in later stages of the illness appear grotesque. The rigid form, often referred to as the Westphal variant, involves muscular rigidity, slowness of movement, tremor, and the bent-forward posture features usually seen in Parkinson disease but not in the choreic form. Mental deterioration is similar in both types.

A staging system for HD that is based on the patient's functional ability has been proposed [10]. This system classifies patients according to their capabilities in the area of work, fiscal management, social and emotional roles, and activities of daily living. The first of the five stages includes diagnosed patients showing no functional deficits with regard to activities of daily living who remain employable

in their present occupation. At the next stage, the patient is employed, but at a lower level of capacity and can manage his or her daily affairs. In the third stage, he or she is unemployed and can no longer manage household responsibilities but activities of daily living may be only marginally impaired. In stage four, the patient is no longer independent in activities of daily living but is capable of being supported by the family. In the final stage, the patient can no longer function independently and requires complete support in all activities of daily living.

The most common cause of death in HD is cardiovascular disease and pneumonia following general debility from incessant choreic movements. Choking secondary to aspiration of food and suicide are also relatively common causes of death.

GENETIC ASPECTS

Mode of Inheritance

The autosomal dominant inheritance of HD is apparent in family studies. In order to test the autosomal dominant hypothesis, a straightforward segregation analysis cannot be performed due to variable age of onset since all gene carriers cannot be determined with certainty. Reed and Chandler [11], using the maximum likelihood method of Haldane [12] to allow for incomplete ascertainment and correcting for age of onset, found excellent agreement with the .5 expectation under dominant inheritance. Elston et al. [13] performed a segregation analysis of data from 11 HD families comprising 430 individuals and one large 7-generation pedigree with 559 individuals. Age of onset was assumed to be normally distributed. The Mendelian dominant hypothesis fit both data sets ($P < .5$ and $P < .98$) with maximum likelihood estimates for age of onset of 35.6 ± 7.96 for the 11 families and 38.6 ± 10.35 for the single pedigree. Both the Mendelian recessive and environmental hypotheses were rejected ($P < .01$).

Gene Mapping

Attempts to localize the HD gene have until recently been futile. Approximately 30 classic polymorphic antigen and enzyme markers were uniformly negative although they did allow the exclusion of the HD locus from some 20% of the genome [14–17]. Since normally large amounts of family data are required to find a significant linkage in late-age-of-onset disorders, these time-consuming negative studies were frustrating. Recently, in an initial screen of restriction fragment length polymorphisms for linkage to HD, 12 such markers were tested in an American family [18]. Of these markers, only one (G8) gave a suggestion of linkage (lod score of 1.8 at a recombination fraction of zero). Selected members of a large Venezuelan family (to be described later) were then typed using marker G8, and finally the search had ended. Combining the American and Venezuelan families gave a lod score of 8.53 at $\theta = 0$ with a 99% confidence interval of 10 cM. The G8 clone actually detects two closely linked variable fragments and, thus, four haplotypes, and has been assigned to chromosome 4. The frequency of heterozygotes when the four haplotypes are considered is 52%. This finding of very close linkage opens up new avenues in counseling and research in HD. Preclinical diagnosis will now be available to a number of at-risk individuals;

however, the ethical problems of balancing the right to know with placing a premature burden on the at-risk individual by informing him or her that he or she has inherited the HD gene have not been answered fully. In the interim, a mechanism should be initiated to store DNA on key family members who, either being old or in the late stages of the disorder, may not be available in the future when they might be vital for prediction in a relative.

The next step in this area of research involves "walking the gene" with the ultimate goal of defining the abnormal DNA sequence and its resulting polypeptide in the disorder.

Fitness

Fitness is difficult to estimate accurately due to the many factors involved. As Reed and Neel [19] point out, it is the fitness of heterozygotes symptomatic and asymptomatic, not choreics, that is of genetic importance. Thus, another difficulty in estimating fitness peculiar to late-onset disorders is the inability, at any specified age, to recognize a certain fraction of heterozygotes, that is, those who are asymptomatic.

To ensure that the reproduction of individuals in their study was nearly or completely terminated, Reed and Neel [19] included only persons living at age 45 or over or deceased at age 15 or over. Age 15 was chosen because no chorea occurred earlier in their sample. This study group consisted of 120 choreic males, 137 choreic females, and their 97 nonchoreic male and 113 nonchoreic female sibs. The average number of offspring for choreic males was 1.85 vs. 2.07 for normal males. The reverse occurred in females; choreic females averaged 2.82 offspring vs. 2.03 for normal females. Correcting for the fact that a proportion of the nonchoreic sibs are heterozygous, the mean number of offspring for heterozygous males was 1.77; homozygous normal males, 2.22; heterozygous females, 2.69; and homozygous females, 2.11. This study suggests that, while heterozygous males have lower fertility than their homozygous sibs, heterozygous females are more fertile than their homozygous sibs. This is due, in part, to the higher proportion: 26% of "never-married" male choreics compared to 8% for females.

When the above results were compared to census data on the general population of Michigan, it was found that the mean number of offspring for heterozygotes, although greater than their normal sibs, was less than the general population. They estimated fitness relative to the general population for choreics and also for heterozygotes, the latter including affected individuals and a proportion of their normal sibs estimated to be carriers. These estimates are given in table 1. Thus, while the fitness of both heterozygotes and choreics was higher than their normal sibs, they were lower than the population at large. This finding could be explained by a voluntary limitation of reproduction due to the existence of HD within the family. The fitness of heterozygotes (0.82) is one of the highest relative fitnesses described for a rare dominant disorder, due at least partially to late age of onset. Reed and Neel [19] hypothesized that the apparent decreased fitness of choreics may result from earlier termination of reproduction following institutionalization. When age at first institutionalization was used as the end of reproduction, the fitness of heterozygotes increased to 0.93.

TABLE 1

RELATIVE FITNESS OF CHOREICS AND THE HETEROZYGOTES IN MICHIGAN [19]

	Choreics ± SE	Heterozygotes ± SE
Males	0.69 ± 0.12	0.66 ± 0.11
Females	1.02 ± 0.16	0.98 ± 0.15
Mean of males and females	0.86 ± 0.13	0.82 ± 0.12

In a study of 129 Minnesota kindreds [20], choreic females produced a mean of 3.36 children, choreic males 2.48, normal females 2.51, and normal males 2.41. As in the previous study, more choreic males were childless (40%) than choreic females (17%). When compared to the overall Minnesota population, the fitness of choreic males was 0.99 and choreic females 1.39 or a combined fitness of 1.18. These results are difficult to reconcile with the relative rarity of HD.

Mattsson [21] studied fertility on a small sample (113) of HD patients and found a fertility of 0.97 relative to the general population. Shokeir [22] studied the reproductive performance of 157 patients with HD, their 170 normal siblings, and 150 matched unrelated controls in the Canadian prairies. Compared with the general population, the fitnesses of patients and that of their asymptomatic siblings were estimated to be 1.14 and 0.83, respectively. Based on his results, Shokeir suggested that, should the present reproductive pattern continue, the allele for HD would double in frequency (with consequent doubling of the prevalence of the disorder) in 6 generations or approximately 150 years.

Mutation Rate

Two methods, indirect and direct, have been used to determine the mutation rate in HD. Using the indirect method, the mutation rate is given as $1/2\ (1 - f)n/N$, where f is the relative fitness of gene carriers, n is the number of carriers, and N is the total population [23]. In the case of HD, the numbers of carriers (heterozygotes) is unknown but can be estimated using the cumulative age-of-onset distribution. The major problem with this indirect method is estimating fitness; as discussed in the last section, data on fitness are very variable. In some cases, the fitness of affecteds was greater than the general population, which, applying the above formula, would lead to a negative estimate for mutation! Estimates of the mutation rate (per million gametes) based on this method are 0.7 [24], 0.8 [21], 1.5 [25], and 9.6 [19] in Caucasians and 0.33 in Orientals [26].

In the indirect method, the mutation rate is estimated as the number of sporadic cases (those with no previous family history) divided by twice the total population (since each individual is diploid). While this method seems straightforward, it can be prone to errors inherent in the assumptions on which it is based. Because of a variable age of onset in HD, onset may be extremely late in a parent while the disease is manifested many years earlier in an offspring. Reed and Neel [19] give an example of a patient with HD, age 44 years, whose parents were reported normal by the patient's wife and a physician at ages 77 years (father) and 68

years (mother). However, a neurological examination revealed that the father and father's brother had definite although mild symptoms of the disease. This situation is not rare. Misdiagnosis is also possible. Bird [27] reports that 7% of 250 cases diagnosed as HD actually had other neurological conditions on post-mortem examination of the brain. Another assumption is that the isolated case is genetic in origin. While there is no evidence of nongenetic cases of HD, they are known to exist for other diseases, for example, retinoblastoma [28]. Another problem is paternity, that is, the stated father may not be the biological father, and the latter could have transmitted the Huntington gene. Schacht and Gersowitz [29], in a study in Michigan based on blood group markers, found that 1.5% of Caucasian children were extramarital. This figure would undoubtedly be larger if they had available to them the 30 or more marker systems including HLA that are now routinely used to determine paternity. Wendt and Drohm [25] in a study of over 4,000 HD patients found a sporadic case whose parents were advanced in age with no signs of the disease, but blood typing revealed that their only likely mutation was illegitimate.

Direct estimates of the mutation rate for the HD gene tend to be lower than those obtained using the indirect method. They vary (per million) from 0.13 [30] to 4.0 [24], 5.0 [21], and 5.4 [19]. These rates vary 40-fold from low to high. Although this is not uncommon for estimates of human mutation rates, it is probably indicative of the problems previously mentioned rather than a real difference in the mutation rate among different populations. Comparison of these rates with those for other dominant disorders reveal that the mutation rate for HD is among the lowest known for human disorders, probably due in part to the late age of onset [31]. Shaw and Caro [32] summarized data on mutation rates to HD. They suggest that new mutants make up around 0.1% or less of all cases. However, Bundy [33] disputes this low estimate, stating that the true figure is closer to 10%; this high figure would receive little support among geneticists.

NATURAL HISTORY

Duration

One might expect the duration of illness, that is, the interval between onset and death, to vary with age of onset. Shorter survival in an affected manifesting later in life might be expected since his or her overall physical condition at time of onset would be poorer than that of a younger individual. Furthermore, as pointed out by Newcombe et al. [34], age of onset is not a precise variable and an individual in whom it is overestimated would show decreased survival time; thus, one might expect to find a negative correlation between onset age and survival time. Despite these factors, the majority of studies suggest that duration is relatively constant. It does not seem to be affected by either geographical location or sex. Furthermore, age of onset, in general, is not significantly correlated with duration. One possible exception is a study by Currier et al. [35], who found a significant negative linear correlation of age of onset with rate of progression ($r = -.844, P = .0001$) in HD. Their sample, however, was small (21 patients), and it is conceivable that rapid progression may not necessarily reflect shorter

TABLE 2

MEAN DURATION OF DISEASE BY AGE OF ONSET

Age of onset	No. cases	Average duration
0–4	4	8.0
5–9	8	11.75
10–14	9	15.55
15–19	21	17.33
20–24	41	18.09
25–29	75	17.96
30–34	116	17.50
35–39	140	17.96
40–44	122	17.03
45–49	84	14.98
50–54	74	16.20
55–59	35	12.97
60–64	14	15.78
65–69	4	14.25
70–74	4	8.75

duration. Incidentally, they obtained similar findings for hereditary ataxia and Alzheimer disease.

Table 2 gives the mean duration by age of onset in 5-year intervals. It is based on data from 227 affecteds from the National Huntington's Disease Roster based at Indiana University. The overall mean duration is 17.1 years. With the exception of the youngest (9 and under) and oldest groups (over 55), duration appears to be relatively constant.

Cause of Death

Heart disease is usually the most common cause of death in HD. The second most common cause is pneumonia. Reed and Chandler [11] found that, among nonhospitalized patients, 7.8% of males and 6.4% of females committed suicide. Hayden et al. [36] found that suicide accounted for 3.35% of all deaths of affected individuals in South Africa.

PREVALENCE

Prevalence, Incidence, and Mortality

In the case of genetic diseases, one normally estimates the incidence rather than the prevalence of the disorder. A problem arises with dominant disorders with incomplete penetrance or late age of onset, where one cannot directly determine incidence since only approximately one-third of carriers are affected.

One can determine prevalence directly and from this figure estimate incidence. Prevalence measures the frequency of all current cases of a disease within a specific population and is calculated for a given time and a given place. It is usually expressed as a prevalence ratio—the number of persons with the disease at a specific time per 1,000,000 persons capable of having the disease at the same specified time [37].

Unfortunately, complete ascertainment of affected cases is usually not possible for any reasonably sized geographic area. Methods for ascertaining affecteds

differ widely; thus, estimates of prevalence of HD from many different countries are not strictly comparable. Earlier studies counted only admissions to hospitals and mental institutions and therefore gave estimates which were low. In fact, there is a general trend toward increased prevalence rates in more recent epidemiological surveys that tend to ascertain both institutionalized and noninstitutionalized patients.

The use of death records to determine prevalence of HD is not ideal and also may not be accurate. Epidemiologists typically do not use death records to determine prevalence of a disorder unless it is fatal and the duration, from onset to death, is extremely short. HD does not meet the second criterion. The *International Classification of Diseases* in 1968 assigned a separate code, 331.0, for HD in the eighth edition and a code, 333.4, in the ninth edition in 1979. However, only a few countries use this specific code in their death records. Furthermore, although the death certificate allows for the listing of several diseases, which, when acting together, cause the patient's death, routine mortality statistics include only the underlying cause of death when, in fact, several conditions may actually have contributed [37]. Hogg et al. [38] calculated age-adjusted death rates for the entire United States for HD for 1968–1974. The annual rate by state varied from zero in Alaska, Idaho, and North Dakota to 4.09 per million population in South Dakota. Geographically, the mortality rate was highest (1.35 per million per year) in the North Central and West regions and lowest (0.93 per million per year) in the South. The Northeast region had a rate of 1.00 per million per year.

These deaths were mainly among the white population. While 27 states reported deaths for HD among blacks, the death rate in most cases was lower than in whites. The overall rates were 1.22 and 0.38 per million per year for whites and nonwhites, respectively.

Kurtzke [39] summarized mortality data from countries outside the United States. The crude death rate for Sweden for the period 1969–1974 was 1.71 and for Denmark (1971–1975), 1.76 per million population. They pointed out that, due to the Scandinavians' high level of medical expertise, the state-oriented systems of medical care, and the availability of detailed mortality and morbidity data, the above data are as complete and accurate as any in the world. Death rates for England-Wales for 1960–1973 were 1.55 per million population. The death rate in Japan (0.13 per million population) was approximately one-tenth the values from the Western Hemisphere.

Another method of determining prevalence is based on morbidity data, that is, attempting to ascertain all affected individuals in the area. Individual cases may be ascertained by standard survey methods, which, in the case of HD, involve records from nursing homes, veterans hospitals, and mental institutions and other hospitals as well as disability records where available. In the case of a dominant disorder such as HD, this approach is usually supplemented by seeking out families of probands and obtaining an extensive family history. Published family histories are not suitable in this regard as it will normally not be possible to determine whether all patients live in the specific area; if they are, in fact, living; and, in some cases, whether a proportion of those classified as not affected may show signs of the disorder. Sporadic cases, with a negative family history, are particularly

difficult; in the absence of confirmed brain pathology, including radiologic methods, it is virtually impossible to be sure of the diagnosis.

Earlier prevalence studies, for example, the well-known study [40] in East Anglia in England in 1934, were based solely on the number of affecteds in mental institutions. Since a large proportion of affecteds are never admitted to a mental institution, these early studies resulted in underestimation of the true frequency. In general, later studies on prevalence included other sources including physician and nursing home records and extended family histories and thus are higher and more accurate. With the exception of a few isolates where the prevalence of HD is very high (these will be discussed later), the greatest prevalence is found in Western Europe including the United States, Canada, Australia, South Africa, and populations of similar ancestry. Table 3 gives prevalence data for different geographical regions, all Caucasian. Since there is extensive literature on prevalence of HD, only representative data are given, including more recent studies and those with a relatively large population base. Among the data listed here, those from South Wales [46] are probably the closest to complete ascertainment. A more detailed summary of prevalence data is given by Hayden [51].

Prevalence data on non-Caucasian populations are scant but in all cases are less than those in Caucasians. Reed and Chandler [11] ascertained three black patients in their Michigan study for a prevalence of 15 per million. Beebe [52] studied discharged veterans from V.A. hospitals. Based on the racial distribution of all V.A. hospital discharges in 1973, he estimated that the frequency of HD among blacks was approximately one-third that among whites. Hayden and Beighton [53] found only three African blacks affected in a population of 19 million for a

TABLE 3

PREVALENCE (PER MILLION) OF HD IN CAUCASIANS

Area	Prevalence	Reference
United States:		
Minnesota	54	[41]
Michigan (Lower Peninsula)	42	[11]
Canada:		
Manitoba	84	[22]
United Kingdom:		
Northamptonshire	63	[42]
Western Scotland	52	[43]
Bedfordshire	75	[44]
Yorkshire	42	[24]
East Anglia	92	[45]
South Wales	76	[46]
Europe:		
Germany	27	[25]
France	70	[47]
Belgium	16	[48]
Sweden	47	[21]
Australia:		
Victoria	46	[8]
Queensland	63	[49]
South Africa	22	[50]

prevalence of 0.16 per million, suggesting that the African HD gene is rare. This is confirmed by the U.S. data if white admixture in black Americans is considered. Reed [54], using the Duffy blood group and Gm, estimated that northern U.S. blacks have 20%–28% white admixture. Using an average of 24%, we might expect that the prevalence of the Huntington gene in blacks would be $.76\ q_a + .24\ q_c$, where q_a and q_c are the prevalence of HD in African blacks and Caucasians, respectively. Considering the paucity of data on blacks, we therefore cannot exclude the possibility that no black mutation for the HD gene exists.

The disorder is also rare in Orientals. In the Aichi prefecture of Japan, 13 HD patients were found in a population of 3.9 million, giving a prevalence of 3.3 per million [26]. Narabayashi [55] reviewed 42 Japanese publications on HD and reports that the disorder has been found in all regions of his country. Three families with HD were reported in Central Taiwan [456]. Scrimgeour [57] reported on two Melanesian families from Papua New Guinea with HD. Although he could not rule out the possibility that the gene might be Caucasian in origin, all members of both families appeared to be Melanesian and blood typing gave no evidence of Caucasian admixture.

There are a number of areas with an unusually high prevalence of HD. In Tasmania, Brothers [58] ascertained 105 patients in a population of 60,344, a prevalence of 174 per million. He was able to trace the original source of the gene to a woman who emigrated with her 13 children from the United Kingdom in the middle of the last century. The most interesting area of high prevalence is in the state of Zulia in western Venezuela. This population was first described by Negrette in 1963. In 1973, Avila-Giron [7] reported 28 living cases (2.07% of the population). The mean age of onset was 31.9 (range 23–54). Retrospective history revealed 203 choreic deaths in these same families. A search for the affected parent revealed that the defect was inherited from the mother in 48.4% of cases, from the father in 21.8%, and from both parents in 29.8%. This latter observation, with the possibility of detecting a homozygous affected, has led to further studies in the area. A recent study of this population found that practically all of the affecteds can be linked into one kindred with over 2,000 individuals and over 50 living affected members [59]. Bonilla et al. [59] ascertained 17 individuals whose parents both had HD. None had unusual neurologic findings, suggesting that, if homozygotes survive to birth, the HD gene may be a true dominant, that is, the homozygote is not clinically distinguishable from the heterozygote.

Heterozygote Frequency

The frequency of heterozygotes and the resulting gene frequency are of interest to geneticists. Since heterozygotes cannot be identified before onset, the method of estimation must be indirect. A number of methods have been used to estimate the frequency of heterozygotes. The simplest and most efficient is given by [11]. If H is the number of observed affecteds in an area at time t, P_x is the proportion of affecteds whose chorea is recognized by age x, and N_x is the total number of individuals of age x, then the frequency of heterozygotes (f) in the area at time t is:

$$f = \frac{H}{\sum_x N_x P_x} .$$

P_x is estimated from the age-of-onset distribution, and the summation is over all ages. Using this formula, Reed and Chandler [11] estimated the frequency of heterozygotes in the Lower Peninsula of Michigan to be one in 9,900 individuals. Since their prevalence rate was 41 per million, this means that only about 40% of heterozygotes were identified as such. In a study of HD in South Wales, the prevalence was estimated at 7.55 per 100,000 and the total heterozygote frequency at 20.2 per 100,000 [46].

Frequency of At-risk Individuals

To my knowledge, no investigator has attempted to directly ascertain the number of at-risk individuals in a population, although studies on fertility of affecteds such as that by Reed and Neel [19] ascertained all offspring of affecteds. Since the number of at risks at birth is twice the number of heterozygotes, a rough estimate of at risks can be determined by subtracting the number of affecteds from twice the frequency of heterozygotes. These calculations result in an underestimate since a similar life expectancy for affecteds and their normal sibs is assumed. A more accurate estimate could be obtained using life tables to correct for differences in life expectancy. Ascertainment of the number of at-risk individuals in a population is important since they should have access to genetic counseling and also could benefit from long- or short-term psychological counseling [60]. It is possible to approximate the number of at-risk individuals as follows. Since approximately one-third of heterozygotes are affected at any given time (two-thirds are unaffected gene carriers), and a number of homozygotes equaling the number of heterozygotes are also at risk, there are approximately five times as many at-risk individuals in a population as there are affecteds.

AGE OF ONSET

One of the most interesting facets of the natural history of HD is its variable age of onset. Although the disorder is inherited as an autosomal dominant, its clinical manifestation may occur any time from the neonatal period to age 70 or older.

Precise definition of age of onset is difficult. One must normally rely on information gleaned from relatives or use age at first diagnosis by a physician. Both methods are biased. Information from relatives will depend, for example, on their relationship, both biological and social, to the affected and their familiarity with the disease. Using age at diagnosis is problematic because many patients in the early stages of the disorder are in the denial stage and will not seek medical help even at the insistence of their families. The length of the denial stage is quite variable; thus, age at first diagnosis may be of less value than a retrospective report from a spouse or relative.

Julia Bell in 1934 [9] published a classical study on HD with an emphasis on age of onset, its variability, and correlations among relatives. The mean age of

onset was 35.51 years for 460 affecteds in Britain. Reed and Chandler [11] in their Michigan study found a mean onset of 35.30 for 204 affecteds; Panse [61] studied 446 affecteds in Germany with a mean onset of 36.19. Data from the National Huntington's Disease Roster at Indiana University give a mean onset of 36.11 years for a total of 999 affected individuals. With the exception of one study [62], most estimates of age of onset are very similar to the above. Wendt [62] reported a mean age of onset of 43.97 years in 760 affected individuals in Germany. This is significantly higher than all other large studies. Myrianthopoulos [63] suggested that the reason for this considerably higher mean age of onset is due to the fact that Wendt did not use recent sibships with relatively young individuals since they would necessarily include only those affected individuals with early onset. It is unlikely, however, that this explanation could account for this large difference in mean age of onset. No significant differences in onset age between males and females have been observed in any of the studies.

A number of investigators studied correlations of age of onset among various relatives. Bell [9] found a sib-sib correlation of .64 and parent-offspring correlation of .50. However, Reed and Chandler [11] found a significantly lower sib-sib correlation of .28. Bell realized that a bias existed in her data due to utilization of incomplete histories in which sibs who become choreic later are counted as normal. Myers et al. [64] found a parent-to-child correlation of .78 with each child treated separately. Pericak-Vance et al. [65] divided their data into two groups, those with a proband with juvenile onset (65 families) and those with an adult-onset proband (89 families). Using covariance analysis, they found a significant difference in age of onset between the two types. Later, Pericak-Vance et al. [66] used maximum likelihood methods to study age-of-onset heterogeneity among families. Both age of onset and age at examination were used in calculating an individual's likelihood of being affected. They found that the existing variation in age of onset between juvenile- and adult-onset families is dwarfed by the magnitude of the variation among the families within each type. They suggested, on the basis of these results, that families of sufficient size should be evaluated individually for age of onset for the purpose of either genetic counseling or linkage studies.

Factors Affecting Age of Onset

One of the most perplexing features of HD is the variable age at which symptoms, either psychiatric or neurological, first appear. There are two separate aspects to this phenomenon—the first is the overall variability in age of onset in HD that is shared by a number of other autosomal dominant neurological disorders including myotonic dystrophy and the ataxias. The other aspect is unique to HD and concerns the excess of paternal transmission among affecteds with juvenile onset. These will be dealt with separately.

There are several theories on the overall variable age of onset in HD, which may be subdivided into four general categories: (1) genetic modifiers, (2) environmental threshold, (3) disturbed-tolerance autoimmunity, and (4) maternal protection. These models are not necessarily mutually exclusive. For example,

the maternal-protection model is invoked to account for the excess of paternal transmission among juveniles and may not be primarily responsible for the overall variability in age of onset.

The first model hypothesizes that one or more loci independent of the HD locus act together with the HD gene to cause variable onset. This would account for the significant within-family correlation for age of onset. Haldane [67] showed that if a late-onset disease is determined by a single gene and a number of modifiers, sib-sib and parent-offspring correlations would approximate .5. Harris and Smith [68] noted that these correlations could be substantially higher than .5 if several independent mutant genes, each with characteristic onset distribution, are postulated for the trait. Multiple alleles or multiple loci alone cannot account for the heterogeneity in onset observed within families since all affected members in a given family share the same HD gene.

How might modifying genes for onset act? An intriguing hypothesis has been suggested by Finch [69]. He proposes that the striking increase in HD in midlife reflects an interaction of the HD gene with normal age changes in the basal ganglia. He further suggests that the latter changes are genetic in origin, a fact which has been demonstrated in inbred mice [70, 71]. In other words, HD gene carriers who have "superior aging genes" would be expected to show symptoms much later in life than those with "inferior aging genes." If this hypothesis is true, one would expect a high correlation between age of onset in affecteds and age at death in their normal sibs.

Went et al. [72] studied 102 families with 1,100 patients with HD in the Netherlands. They compared the mean age at death for patients, the nonaffected parents, and sibs within and among families. They found that the variation of the mean age of death between families as compared with the variation between individuals was highly significant and concluded that this was due to genetic heterogeneity. When affecteds and their normal parents and sibs were compared, they found little difference if the affected died when old but a much greater difference if the affected died at a young age. They did not, however, calculate correlation coefficients for age at death in affecteds and in their normal parents and sibs. Farrer et al. [73], in a study of longevity parameters in HD, evaluated 214 families with normal and affected individuals. The correlation between mean age of onset in affecteds and mean age at death in their normal sibs was .52. The correlation for age of death in the affected parent and mean age of death in the normal offspring was .57. These results agree with the hypothesis that "aging genes" may be responsible for the variability in age of onset in HD.

The environmental threshold model assumes that the genotype (in this case the Huntington gene) is modified by specific environmental factors. If we assume that a large proportion of an individual's genes are inactive at any given time, it follows that the environment could initiate physiological processes that may activate or deactivate parts of the genome. These environmental factors include hormones [74], climate [75], occupational stress [76], and stress in general [77]. These studies are difficult to assess. For example, the study on stress was anecdotal, providing evidence that traumatic life situations precipitate onset of HD. The data on occupational stress classify occupations into three grades according to

increasing occupational stress. A furniture maker is in grade 1 (least stressful) while a bricklayer is in grade 3 (most stressful), a distinction which is somewhat difficult to understand. The climate data suggesting that lower temperatures precipitate onset earlier was based on geographical data and has not been confirmed by other studies.

The disturbed tolerance-autoagressive disease model has been proposed by Burch [78]. He suggests that late-age-of-onset disorders such as HD are initiated by a specific set of random events. These random initiating events are specific somatic gene mutations in one or more stem cells of the central nervous system. A mutant stem cell propagates a "forbidden clone" of descendant cells, and they or their secreted humoral products attack target cells that bear complementary recognition macromolecules. When the severity of the autoregressive attack on target cells progresses beyond a certain threshold, symptoms and signs of disease become manifest. He states that hereditary distinctions (e.g., familial correlations) are due to modifying genes. This hypothesis has yet to be tested.

The effect of paternal sex is one of the more interesting features of onset in HD with a large excess of paternal transmission in juvenile cases. Merritt et al. [79] were the first to report that in the juvenile form (onset before age 21) the father is the affected parent approximately four times more frequently than is the mother. In 106 sibships with at least one juvenile offspring, the sex ratio of affected parents was 84 male:22 female. These findings have been confirmed by numerous investigators [53, 80–84]. Recent data from the National Huntington's Disease Roster show no significant difference in age of onset in males vs. females. The mean age of onset in all offspring of affected males is 3.5 years earlier than in offspring of affected females, suggesting that this phenomenon is not confined to the juvenile. Figure 1 gives the overall distribution and figure 2 the cumulative

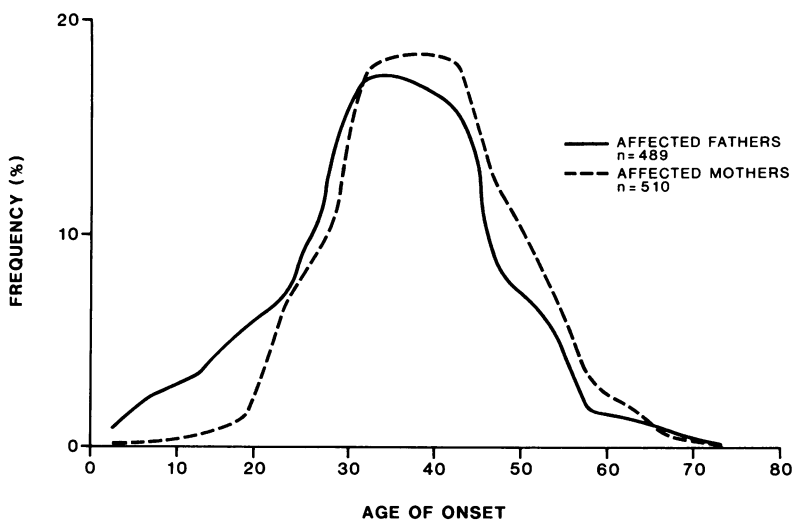

FIG. 1.—Age-of-onset distribution for offspring of affected fathers vs. affected mothers

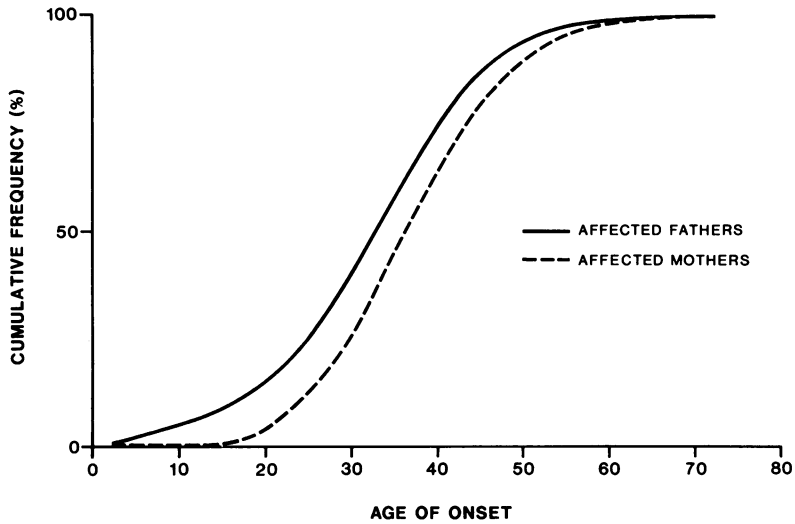

FIG. 2.—Cumulative frequency of age of onset in offspring of affected fathers vs. affected mothers

distribution of age of onset in offspring of affected males and affected females. The distribution for offspring of affected males is shifted to the left when compared with offspring of affected females. Since these differences are significant, separate probabilities of being carriers for offspring of affected males and females should be utilized. The conditional probability (P_x) of having inherited the gene, given that the individual is unaffected at age x, is given as: $P_x = (1 - C_x)/(2 - C_x)$, where C_x is the probability of being affected by age x given that the individual carries the gene.

A number of theories have been proposed to explain this anomalous inheritance. Jones [85] suggested the possibility that the HD fetus with the potential for early onset succumbs in utero if the mother is affected, due to a reaction between the choreic or, more likely, at-risk mother and the fetus. If the father is the gene carrier, there is no opportunity for such a reaction to occur. Other theories include a modifying gene on the X chromosome [24] or a Y-linked gene [52] and ones based on the social impact of the disorder on carriers [78, 86].

None of the above theories has proved to be satifactory. Wallace [87] proposed a cytoplasmic protective factor, possibly a mitochondrial gene transmitted by the mother to all of her offspring. Boehnke et al. [88] considered this model and a second one that assumed that the protective factor was an allele at an autosomal or X-linked locus with the maternal genotype modifying age of onset in her offspring. They presented a mathematical formulation for the cytoplasmic factor model using data on age of onset from the National Huntington's Disease Roster. Both models, cytoplasmic and chromosomal, predict both differential age of onset depending on the sex of the transmitting parent and more pronounced anticipation (earlier onset in child than in parent) in the male line. Children of affected fathers had onset approximately 4 years earlier than children of affected

mothers. This difference was highly significant. There was no effect due to sex of the affected child or to parent sex-child sex interaction. Anticipation averaged 8.06 years when the father was affected but only 1.41 years when the mother was affected. A second prediction stemming from both models is a higher correlation for age of onset in affected mother-child pairs than in affected father-child pairs. These correlations were found to be .730 for mother-child pairs (no. = 281) and .562 for father-child pairs (no. = 276). The difference between these correlations is highly significant ($Z = 3.44$, $P < .001$) on a two-tailed test.

We might assume that the observed excess of affected fathers among juvenile cases could be responsible for both differential anticipation and parent-offspring correlation on the basis of parental sex. Boehnke et al. [88] found that this was not the case. When they excluded juvenile-onset cases, anticipation averaged 5.65 years in the case of paternal transmission and only 0.90 years for maternal transmission. The father-offspring and mother-offspring age-of-onset correlations were .439 and .714. Both of the differences were highly significant. These results strongly suggest that either the maternal nuclear or cytoplasmic genotype protects her carrier offspring and causes delayed onset. Their results could not distinguish between the two models.

Myers et al. [84] also studied the effect of maternal transmission on age of onset. They found that among 205 affecteds, 91% of juvenile cases, 66% of early-onset, 43% of midlife onset, and 29% of late-onset inherited the gene from an affected father, the remainder in each case inheriting the gene from their affected mother. This led them to suggest a model where the late-onset form of HD is related to a maternally transmitted factor such as the mitochondrion and its genome.

In summary, the more plausible explanations for variability in age of onset are twofold. First, the general variability may be independent of the HD gene. Affected individuals with "superior aging genes" would be expected to have onset significantly later in life than those with "inferior aging genes." Second, the specific phenomenon of excess paternal transmission among juvenile-onset cases can best be explained by either a maternal protective factor in the cytoplasm (possibly a mitochondrial gene) or a maternal genotype that affords protection.

BIOCHEMISTRY

Huntington disease is primarily a disorder of the central nervous system but the defect is also expressed in other areas. Whether the disorder is due to a membrane defect or an enzymatic defect leading to an increase (or decrease) of a specific product is unknown. Studies on membrane defects have led to seemingly conflicting results. Following a report [89] that HD fibroblasts grew poorly in culture, a number of investigators found the opposite [90–92]. Later, using a double-blind study, one of the previous investigators [93] was unable to find any differences between HD and control fibroblasts. Studies on electron spin resonance of red cell ghosts [94], ANS fluorescence probe-binding in fibroblast membranes [95], and glutamic acid uptake by fibroblasts [96] showed differences between controls and HD patients but did not hold up under critical scrutiny by independent investigators [96–98]. This led Comings [99] to write an editorial entitled "The

Ups and Downs of Huntington Disease Research," in which he made a plea for more precise experimental design before research is undertaken.

Investigations in the area of neurochemistry have found several differences between HD patients and controls. Decreased amounts of the neurotransmitter GABA are present in specific areas of HD brains as is choline acetyltransferase, dopamine, and homovanillic acid, as well as a number of peptides including substance P and angiotensin-converting enzyme [100]. More recently, attention has focused on receptors. Dopamine D-1 and D-2 receptors have been shown to be reduced in HD [101].

The use of two-dimensional gel electrophoresis to search for an altered protein in HD has been negative [102]. Recently, Goldman and Merril [103] found polymorphisms among 186 soluble lymphocyte proteins utilizing two-dimensional electrophoresis of ^{14}C-labeled phytohemagglutinin-stimulated human lymphocyte proteins. Perhaps this technique also may be useful in locating an altered product in HD.

In summary, although major advances in understanding the pathophysiology of HD have been achieved, the underlying mechanism is still elusive. This research has also served another purpose, as it has also benefited research in other neurological disorders with features common to Huntington disease.

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